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Abstract

FBXW7 E3 ubiquitin ligase ameliorates insulin sensitivity in equine metabolic syndrome-affected liver by targeting Fetuin-A hepatokine †

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Abstract: Fetuin-A is a multifactorial glycoprotein predominantly produced by liver but also found in adipose tissue, and tightly regulated by the FBXW7 E3 ubiquitin ligase. Recently, the hepatokine has been implicated in the pathogenesis of insulin resistance and associated metabolic failures in humans through its potent and selective inhibitory effect on tyrosine kinase activity of insulin receptor, however, no reports related to its implication in equine metabolic syndrome onset have been published yet. In this investigation, the effect of FBXW7 E3 ligase on the Fetuin-A/INSR axis has been evaluated. EMS affected liver tissue exhibited significant elevated Fetuin-A levels at protein and mRNA level over lean samples. Moreover, increased Fetuin-A was accompanied by augmentation of circulating levels of IL-1β and TNF-α pro-inflammatory cytokines. Interestingly, liver FBXW7 levels inversely correlated with high Fetuin-A concentrations, and was sensibly downregulated under EMS condition. Treatment of liver explants with exogenous FBXW7 protein resulted in a marked depletion in total Fetuin-A protein expression, which subsequently restored insulin signal transduction via increased INSR phosphorylation. Conclusion: On the whole, EMS affected horses display abnormal high Fetuin-A levels and suppressed FBXW7 expression, which could serve as a new potential therapeutic target for insulin sensitivity restoration in EMS.

Keywords: Fetuin-A; FBXW7; Insulin Resistance; EMS; INSR; Ubiquitination; Liver

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